*The Effect of Structure upon Polarographic Behaviour. Part I. The Depolarisation Potentials of Girard-*T *Compounds.*

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The half-wave potentials of the polarographic reduction of the Girard-T compounds of various dialkyl ketones have been measured at 25° in 50% ethyl alcohol buffers at pH 8·0. The results suggest that the electrode process is basically similar to that proposed by Prelog and Häfliger (*Helv. Chim. Acta*, 1949, **32**, 2088). An interpretation of the relative values of $E_{\frac{1}{2}}$ in terms of electronic and steric effects indicates that the branched alkyl groups (Pr^i, Bu^t, and Bu^i) here display steric hindrance, whilst some indication of a similar effect from Pr^n and higher normal groups is found in suitable structures.

PRELOG AND HÄFLIGER (*Helv. Chim. Acta*, 1949, **32**, 2088) measured the half-wave potentials of the Girard-T derivatives of the C_5–C_{20} cyclanones, demonstrating conformity to the Ilkovic equation and the existence of a two-electron reduction process from the current–potential waves obtained by conventional methods. Moreover, the relative values of these potentials were found to be consistent with the progressive development of a folded ring configuration in the ketones which confers a greater relative stability upon the medium-sized compounds (*ca.* C_9), an effect previously suggested to explain the trend

shown by the ketone cyanohydrin dissociation constants of the same compounds (Prelog and Kobelt, *Helv. Chim. Acta*, 1949, **32**, 1187). Evans and Young (*J.*, 1954, 1310) have shown that the dialkyl ketone cyanohydrin dissociation equilibrium is susceptible to electronic and steric effects from the alkyl groups, and the polarographic reduction of the Girard-T compounds was studied with a similar point in view.

EXPERIMENTAL

Preparation of Ketones.—These were prepared as described by Evans and Young (*loc. cit.*).

*Preparation of Girard-*T *Compounds.*—Girard-T reagent (0·3—0·6 mmole) was refluxed for several hours with the ketone ($\frac{1}{3}$ mol.) added as a 0·1M-solution. These solutions (1—2 ml. in volume) were contained in glass-stoppered test-tubes and were locally electrically heated. When the stopper was strapped in, the upper part of the tube served as an air condenser for the totally enclosed system and smooth refluxing at 110—130° could be carried out for many hours with no loss of solvent and without the inconvenience of sealing off. After reaction, the solvent was removed under vacuum, leaving a white crystalline solid or a clear syrup. Sufficient ethyl alcohol was added to give a 0·01M-solution of the complex based on the original ketone, together with excess of Girard reagent; 0·5 ml. of this solution was added to 9·5 ml. of previously deoxygenated buffer solution, and hydrogen gas (presaturated with ethyl alcohol) was again passed for a few minutes before a manual polarogram was taken.

The buffer solutions were prepared by mixing two solutions, A (0·08M in each of boric, phosphoric, and acetic acids, and 0·4M in potassium chloride) and B (0·4M in each of potassium chloride and hydroxide), and diluting the mixture with an equal volume of absolute ethyl alcohol. A pH 8·0 buffer is given by 20 ml. of A, 14·5 ml. of B and 34·5 ml. of alcohol, this formulation being essentially that of Britton and Robinson (*J.*, 1931, 1456) with potassium hydroxide instead of sodium hydroxide, 50% ethyl alcohol instead of water, and the addition of 0·2M-potassium chloride in the final solution.

The whole procedure above differs only in minor ways from that used by Prelog and Häfliger (*loc. cit.*) and was adopted for the same reasons. The only important difference is the use of ethyl in place of methyl alcohol.

The standard conditions of polarography were: Temp., 25° (jacketed cell); anode, normal calomel electrode; mercury head, 35 cm. over a 0·01-mm. capillary; drop time, 2·8 sec.; drop weight, 8·24 mg./drop at −1500 mv applied potential.

The potentiometer was calibrated before each measurement against a Doran Potentiometer Type 4246 at 1000 mv, and subsequently recalibrated at every 100 mv in the inflexion range. The currents were measured on a Pye Galvanometer Type 7972 damped by an Ayrton shunt of 1060-ohms resistance, which made the maximum sensitivity 0·0585 μA/scale division.

The results in all cases were obtained from the corrected current–voltage curves given by subtracting the residual current for the buffer from the observed current at each potential. The half-wave potentials, $E_{\frac{1}{2}}$, reported refer in all cases to a complex concentration of $5\cdot0 \times 10^{-4}$M, are relative to the normal calomel electrode, and are the means of at least two separate determinations.

The accuracy of these potentials, estimated from the reproducibility in individual cases, is ±10 mv. The values for five measurements on the compound from *n*-hexyl methyl ketone (separate preparations) are given below:

$-E_{\frac{1}{2}}$ (mv)	1488	1490	1487	1501	1511	Mean 1495
i (μA)	2·82	2·82	2·61	2·40	2·40	Mean 2·61

Spectrographic Measurements.—The ultraviolet absorption spectra were determined in absolute ethyl alcohol at room temperature by means of a Unicam S.P. 500 spectrophotometer. The results are given in the Table on p. 1518.

Effect of pH *on the Depolarisation Potentials.*—The variation of the wave form with pH was determined under the standard conditions of polarography for the complexes of *n*-butyl methyl, *tert.*-butyl ethyl, *tert.*-butyl *n*-propyl, di*iso*propyl, and di*iso*butyl ketones. The general observations were: (*a*) At pH's lower than *ca.* 6 the waves become complex, showing two steps. (*b*) The total wave height passed through a maximum at pH 5—7, though the effect was less pronounced for *tert.*-butyl *n*-propyl and di*iso*butyl complexes. (*c*) The waves for di*iso*butyl and *tert.*-butyl *n*-propyl complexes, which are too ill-defined to be measured at pH 8·0, sharpen considerably at lower pH's, but are still relatively ill-defined.

Depolarisation potentials in pH 8·0 *buffer at* 25° *(concn.* 5 × 10⁻⁴M).

Ketone (R·CO·R')					Ketone (R·CO·R')				
R	R' *	$-E_{\frac{1}{2}}$ (v)	i_D (μA)	n	R	R' *	$-E_{\frac{1}{2}}$ (v)	i_D (μA)	n
Me	Me	1·50	3·10	1·5	Et	Pri	1·55	1·64	0·8
Me	Et	1·51	2·81	1·4	Et	But	1·60	0·76	0·4
Me	Prn	1·51	2·75	1·3	Et	C_6H_{11}	1·54	2·34	1·2
Me	Pri	1·54	2·22	1·1	Prn	Prn	1·55	1·57	0·8
Me	Bun	1·51	2·98	1·5	Prn	Pri	1·57	1·05	0·5
Me	Bui	1·57	3·10	1·6	Prn	But	No wave at pH 8·0		
Me	But	1·55	1·29	0·7	Prn	C_6H_{11}	1·56	0·82	0·4
Me	n-C_5H_{11}	1·51	3·34	1·7	Pri	Pri	1·55	1·05	0·5
Me	n-C_6H_{13}	1·50	2·61	1·3	Pri	But	No wave at any pH		
Me	C_6H_{11}	1·54	2·81	1·5	Pri	C_6H_{11}	1·56	0·82	0·4
Et	Et	1·52	2·40	1·2	Bui	Bui	No wave at pH 8·0		
Et	Prn	1·53	2·28	1·1	*cyclo*Hexanone		1·47	3·98	2·0

* C_6H_{11}-*cyclo*Hexyl.

None of these values has been corrected for the iR drop over the cell. Prelog and Häfliger found E_1 for *cyclo*hexanone at pH 8·0 to be 1·48 v (corrected from their pH 8·2 value); they also reported alkyl ketones as having $E_{\frac{1}{2}}$ of *ca.* 1·56 v at pH 8·2 with lower i_D's than *cyclo*hexanone.

The graphed results show that $E_{\frac{1}{2}}$ is not a good linear function of pH [d($-E$)/d(pH) decreases as pH increases]. Two approximately parallel plots were obtained for the first and second steps of the di*iso*butyl and *tert.*-butyl n-propyl compounds, whilst the points for the single waves of the other compounds (excluding that of di*iso*propyl ketone) lie on the curves for the first step of the double waves. The di*iso*propyl compound is slightly anomalous since its slopes are closer to the theoretical value (0·059 v/pH) than any others, and the point for the single wave at pH 8·0 lies closer to the plot for the second (the more negative) wave, whilst the wave separation is observed as high as pH 7·0. The slopes for the approximate straight lines through these plots are :

			di-Pri		But Pra		
	Bun Me	But Et	1st	2nd	1st	2nd	di-Bui
$-dE$/dpH (v/pH) ...	0·10	0·08	0·06	0·06	0·08	0·07	0·08
$-E_{\frac{1}{2}}$ (v) at pH 7 ...	1·44	1·55	1·31	1·55	1·31	1·55	1·31

Analysis of the individual wave profiles by plotting $-E_{applied}$ against log $i/(i_D - i)$ produced reasonably straight lines with slopes greater than theory for a reversible one-electron process (*viz.*, 0·059 v). There was no marked dependence of slope on pH; the values for the n-butyl methyl ketone compound were

pH	5·3	6·0	7·0	8·0	9·0
$-dE_{app.}$/d log $i/(i_D - i)$	0·066	0·068	0·064	0·059	0·062

The wave for the *cyclo*hexanone compound at pH 8·0, when similarly treated, gave a value of 0·062 v, which compares with 0·046 v found by Prelog and Häfliger at pH 8·2 in a methyl alcohol solvent. The values of $E_{\frac{1}{2}}$ obtained from these plots were in all cases equal to those found by tangents drawn on the original waves and the latter method was used in all other cases.

Application of Ilkovic's Equation.—In several instances the dependence of i_D upon the complex concentration at pH 8·0 was demonstrated for small concentration ranges. Ilkovic's equation, $\bar{i}_L = 605nD^{\frac{1}{2}}cm^{\frac{2}{3}}t^{\frac{1}{6}}_{max.}$, was applied to all waves at pH 8·0, it being assumed that (*a*) that the *cyclo*hexanone compound has a two-electron wave as shown by Prelog and Häfliger, and (*b*) that the D's for all complexes were similarly related to D for *cyclo*hexanone *via* their molecular weights. The values of n so found are reported in the Table above.

The variability of n reflects the variability of i_D since the molecular weights of all the complexes are of a similar magnitude. All the values are less than 2, which agrees with an isolated observation by Prelog and Häfliger concerning alkyl ketones. The results fall into two groups : (*a*) where $n > 1$ and ⪬ 1·4, and (*b*) where $n < 1$ and ⪬ 0·6. It is thought that the lower values of the second group may indicate incomplete complex formation.

Tests for Completeness of Complex Formation.—The failure of the *tert.*-butyl *iso*propyl ketone compound to show a reduction wave at any pH while the waves of *tert.*-butyl n-propyl and di*iso*butyl compounds are separated from the background at pH's below 7·0, led to the following tests.

The ketones COBut Me (12), COBun Me (8), COBut Et (22), COBut Prn (22), COBut Pri (36),

and $COBu^i_2$ (16) were subjected to the normal procedure for compound formation, being refluxed for the number of hours shown in parentheses, which were sufficient to give constant diffusion currents in subsequent polarography. The distillates from the vacuum-evaporation were trapped in a solid carbon dioxide–acetone trap and, after suitable dilution with ethyl alcohol, were spectrographically analysed for free ketone. The residues, consisting of compound and excess of Girard-T reagent, were diluted with ethyl alcohol to a concentration of 1.25×10^{-4}M with regard to the Girard compound, complete reaction being assumed, and an ultraviolet spectrum taken. In the Figure these spectra are compared with the spectrum of 3.75×10^{-4}M Girard-T reagent which was unaffected by the refluxing with alcohol. Every ketone except *tert.*-butyl *iso*propyl shows a maximum at 220—230 mμ, which is clearly due to the compound. In every case except from *tert.*-butyl methyl and *n*-butyl methyl traces of ketone were present in the distillates. It is concluded that *tert.*-butyl *iso*propyl ketone does not
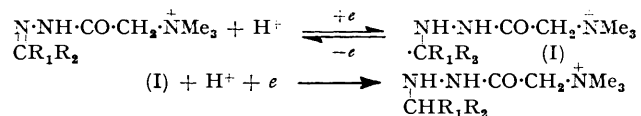
A, Bu^{t}Et. *E,* Bu$^i_2$.
B, Bu^{t}Pr. *F,* Bu^{t}Pr^i.
C, Bu^{t}Me. *G,* blank.
D, Bu^{n}Me.

Wave-length (mμ)
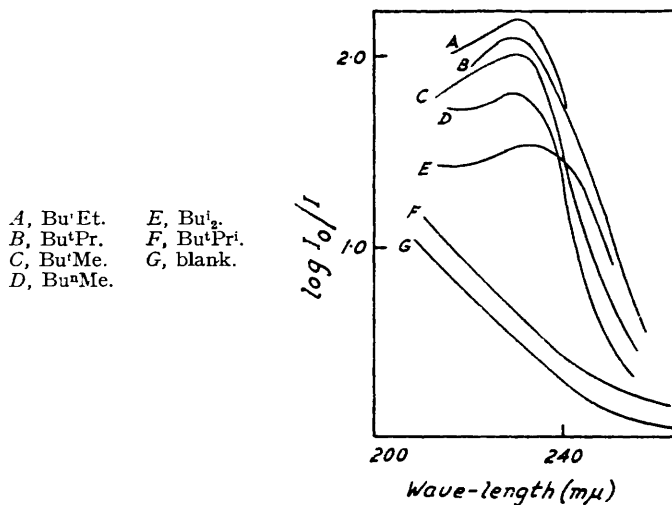
form a compound under the conditions used, whilst the formation may be incomplete, owing to attainment of an equilibrium, in $COBu^tEt$, $COBu^tPr^n$, and $COBu^i_2$.

These results make the reliability of the *n* values in the above Table doubtful, especially when *n* is very low (<0.5). On the other hand, the failure to achieve a Girard compound concentration of 5×10^{-4}M would have no appreciable effect on $E_{\frac{1}{2}}$.

DISCUSSION

The above results present the same general pattern as those of Prelog and Häfliger (*loc. cit.*), *viz.*, the existence of a maximum i_D at *ca.* pH 7.0, the appearance of two steps in waves at pH's below 6.0, and the large slope of the $E_{\frac{1}{2}}$–pH plots are common to both the series of compounds. However, the detail in the alkyl ketone compounds shows a greater variation of type and the departure from the reversible behaviour is wider.

Prelog and Häfliger proposed the following mechanism for the electrode-reduction process by analogy with the mechanism of polarographic ketone reduction (see Kolthoff and Lingane, " Polarography," Interscience Publ., 1952, Vol. II, p. 663, 683) :

$$\underset{\overset{|}{CR_1R_2}}{N}\cdot NH\cdot CO\cdot CH_2\cdot \overset{+}{N}Me_3 + H^+ \underset{-e}{\overset{+e}{\rightleftharpoons}} \underset{\cdot CR_1R_2}{NH\cdot NH\cdot CO\cdot CH_2\cdot \overset{+}{N}Me_3} \quad (I)$$

$$(I) + H^+ + e \longrightarrow \underset{\overset{|}{CHR_1R_2}}{NH\cdot NH\cdot CO\cdot CH_2\cdot \overset{+}{N}Me_3}$$

They supported this choice by isolating the dimer of the radical (I) in preparative experiments. The departures from truly reversible behaviour were ascribed to the irreversibility of the second step.

Berzins and Delahay (*J. Amer. Chem. Soc.*, 1953, **75**, 5716), in a theoretical treatment of

an identical mechanism, find that both the wave profile and the value of $E_{\frac{1}{2}}$ at constant pH depend upon the rate of the irreversible step. Their results, when applied to the present process, suggest that $E_{\frac{1}{2}}$ should vary more rapidly with pH than 0.059 v/pH, as found, but the waves should tend to become single as the pH decreases, in contradiction to the observed changes.

The variation of i_D with pH, which is a feature of the aldehyde and ketone reductions also, and the observation that the double waves of the acid region have sections of approximately equal heights, are not easily explained and invite comparison with the reduction of formaldehyde and acetaldehyde (Vesseley and Brdicka, *Coll. Czech. Chem. Comm.*, 1947, **12**, 307; Bieber and Trumpler, *Helv. Chim. Acta*, 1947, **30**, 706, 1109, 2000), and of glyoxal (Elving and Bennett, *J. Amer. Chem. Soc.*, 1954, **76**, 1412). This survey emphasises the complexity of the electrode process for Girard-T compound reduction and suggests that the reversibility of the first stage is not securely established.

Apart from this indecision concerning the mechanism, the fact that structural influences are operative in determining $E_{\frac{1}{2}}$ seems inescapable. It is assumed that reduction of a Girard-T compound may be reasonably compared with that of a carbonyl compound, and therefore, the conclusions drawn by Davies and Evans (*J.*, 1939, 546) concerning the alkyl phenyl ketones, and by Baker, Davies, and Hemming (*J.*, 1940, 692) concerning the *para*-substituted benzaldehydes, apply here. Thus the reduction is facilitated, and $E_{\frac{1}{2}}$ is decreased, by electron recession from the carbonyl-carbon atom.

Prelog and Häfliger attributed the variation in $E_{\frac{1}{2}}$ in the cyclanone Girard-T compounds to hydrogen bonding between the nitrogen atom and ring-methylene groups. The effect was considered to be sterically favoured by ring folding in the medium-sized ketones (C_8–C_9) which show a maximum value of $E_{\frac{1}{2}}$. The same effect, but involving the carbonyl-oxygen atom, was used by Prelog and Kobelt (*loc. cit.*) to account for the maximum value shown by the cyanohydrin dissociation constants in the same region for the same ketones. In the former case the hydrogen bond stabilises the complex with respect to the radical (I); in the latter, the free ketone with respect to its cyanohydrin.

A similar parallelism is found between the values of $E_{\frac{1}{2}}$ in the Table (p. 1518) and the cyanohydrin dissociation constants (Evans and Young, *loc. cit.*) of the dialkyl ketones. Thus it is roughly true to say that $-E_{\frac{1}{2}}$ is proportional to $K_{35°}$—the cyanohydrin dissociation constant. There is, however, an important quantitative difference between the two series of compounds, as comparable changes of $E_{\frac{1}{2}}$ are accompanied by much larger changes of the dissociation constants in the cyclanone series, *e.g.* :

	Cyclanone				Ketone	
Compound	C_6	C_9		Compound	$COMe_2$	$COBu^tEt$
$-E_{\frac{1}{2}}$ (v) at $20°$	1.51	1.63		$-E_{\frac{1}{2}}$ (v) at $25°$	1.50	1.60
$10^2 K_{22}$	0.1	170.0		$10^2 K_{20}$	2.9	7.3
$\Delta G°_{Diss.}$ (kcal.)	4.2	-0.3		$\Delta G°_{Diss.}$(kcal.)	2.1	1.6

This contrast suggests that there is a difference in kind between the effects operating in the two series.

When the same quantities for the *para*-substituted benzaldehydes, and for acetaldehyde and acetone, are compared, it is found that larger changes of $E_{\frac{1}{2}}$ are linked with smaller changes of K than occur in the alkyl ketones and their Girard-T compounds.

	Benzaldehyde			
Compound	p-Cl	p-OMe	$CH_3 \cdot CHO$	$COMe_2$
$-E_D$ (v)	1.05[a]	1.22[a]	1.87[b]	2.10[c]
$10^2 K_{20}$	0.49[d]	3.1[d]	0.76[e]	2.9
$\Delta G°_{Diss.}$ (kcal.)	3.0	2.0	2.9	2.1

The conditions under which the above E_D's were measured were not identical but this should not invalidate the comparisons. (*a*) Baker, Davies, and Hemming (*loc. cit.*); (*b*) Adkins and Cox (*J. Amer. Chem. Soc.*, 1938, **60**, 1151); (*c*) Stackelburg and Stracke (*Z. Elektrochem.*, 1949, **53**, 118); (*d*) Lapworth and Manske (*J.*, 1928, 2533); (*e*) Jones (*J.*, 1914, **105**, 1506).

It is believed that the simultaneous increases of $-E_D$ and K reported for these compounds are due to the relative degrees of electron release (cf. Baker, Davies, and Hemming, *loc. cit.*), steric effects being absent.

The depolarisation potentials of the Girard-T compounds of the dialkyl ketones are regarded as being controlled by similar electronic (inductive and hyperconjugative) and steric effects to those postulated as determining the extent of the cyanohydrin dissociations for the same compounds (Evans and Young, *loc. cit.*). The magnitude of the electron-release effect is indicated by the sequence of $-E_{\frac{1}{2}}$ for the *n*-alkyl methyl compounds, all of which fall within the range 1·50—1·51 v. Comparison of pairs of compounds containing the normal and branched isomeric groups together with a common group, shows the branched molecule to have an $E_{\frac{1}{2}}$ value 0·03—0·04 v more negative than the normal one. On the basis of electron-release effects alone, the compound containing the normal group would be expected to have the more negative value owing to its potentially higher hyperconjugation effect.

The effects of branching upon the electrode-reduction process and the cyanohydrin equilibrium are revealed by the sequences of $-\Delta E_{\frac{1}{2}}$ and ΔK for ($CORPr^i - CORPr^n$) as R becomes larger, *e.g.* :

	Common group R in the compound :				
$\Delta(Pr^L-Pr^n)$	Me	Et	Pr^n	*cyclo*-C_6H_{11}	Pr^i
$-\Delta E_{\frac{1}{2}}$ (v)	0·03	0·02	0·03	0	−0·03
$10^2\Delta K_{35}$	−3·7	−3·8	−2·5	−0·9	+8·4
$\Delta(\Delta G°)$ (kcal.)	0·3	0·3	0·2	0·1	−0·4

The positive values of $-\Delta E_{\frac{1}{2}}$ indicate that the *branched* isomers are the more difficult to reduce, whilst the common group is *unbranched*. On the other hand the negative values of ΔK show that the *unbranched* ketones are the more stable relative to their cyanohydrins whilst the common group is *unbranched*. It is thought that these situations arise because the cyanohydrin dissociation equilibrium is only markedly susceptible to the steric meshing effect (see Evans and Young, *loc. cit.*) and is electronically controlled throughout the normal group sequence, whilst the electrode process suffers a greater steric impedance from the *iso*propyl than from the *n*-propyl group as long as the common group is smaller than *n*-propyl. Thus the values of $E_{\frac{1}{2}}$ in the Table on p. 1518 show that the decreasing ease of reduction of complexes based on the *n*- and *iso*-propyl groups is di-Pr^n = di-Pr^i > Pr^{i}Pr^n. It therefore seems that the extra electron release from di-Pr^n is equivalent to the additional steric effect in di-Pr^i, while Pr^{i}Pr^n has a steric impedance comparable with that of di-Pr^i with a larger electron release. This conclusion is supported by the pattern of the other results and also by the close similarity of the behaviours of the *cyclo*hexyl and the *iso*propyl group. The alternative to this steric explanation of the results would require anomalous variations among the alkyl-group inductive effects; *e.g.*, EtMe −1·51, EtEt −1·52 v, but Bu^{t}Me −1·55, Bu^{t}Et −1·60 v.

The differences observed among the alkyl phenyl ketones are consistent with this hypothesis, *e.g.*,

$-\Delta E_D$ (Pr^L–Pr^n)	0·03 v	(pH ⇌7) (Davies and Evans, *loc. cit.*)
$10^2\Delta K_{20}$	−65	(Lapworth and Manske, *J.*, 1930, 1976)

where the hyperconjugation of the *n*-propyl group is enhanced by the phenyl nucleus. The failure of the *para*-alkylbenzaldehydes to show the effect is also expected, as no alkyl-group steric effects are present (Baker, Davies, and Hemming, *loc. cit.*; Baker and Hemming, *J.*, 1942, 191). In a similar way the depolarisation potentials of the aliphatic aldehydes (Adkins and Cox, *J. Amer. Chem. Soc.*, 1938, **60**, 1151) are free from any branched-group effect since the alkyl groups are accompanied by the small hydrogen atom on the carbonyl carbon atom.

A greater susceptibility of the cathodic compound reduction to steric influence than is observed in a kinetic equilibrium involving similar structures might be caused by orientation of the compound at the electrode surface. Thus attachment of the quaternary grouping to the mercury surface would leave the variable alkyl groups protecting approaches from the solution side. In this situation attachment of a proton to the doubly-bonded nitrogen atom might meet a higher energy barrier when the alkyl groups are branched. A comparable case of steric impedance has been postulated by Leonard, Laitinen, and Mottus (*J. Amer. Chem. Soc.*, 1953, **75**, 330) to explain $E_{\frac{1}{2}}$ differences, of similar magnitude

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to the present ones, which occur during the reduction of alkane-1 : 2-diones at the dropping-mercury electrode. The standard oxidation potentials of the alkyl ketones determined by Adkins, Elofson, Rossow, and Robinson (*ibid.*, 1949, **71**, 3622) and by Day, Robinson, Bellis, and Till (*ibid.*, 1950, **72**, 1379) are free from any consistent structural effects of the type described above. This may be due to the fact that a kinetic equilibrium process was used for their measurement.

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